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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HAGHIGHATIAN, MINA	
ART UNIT	PAPER NUMBER
1616	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/035,324	BOSCH ET AL.	
	Examiner	Art Unit	
	MINA HAGHIGHATIAN	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9-11 and 13-37* is/are pending in the application.

4a) Of the above claim(s) *15-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7, 9-11, 13-14, 35-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/29/08 has been entered.

Receipt is acknowledged of the Amendments and Remarks filed on 10/29/08. Claims 1, 15 and 35-37 have been amended, no claims have been cancelled or newly added. Claims 15-34 remain withdrawn. Accordingly, claims **1-7, 9-11, 13-14 and 35-37** remain under examination.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-7, 9-11, 13-14 and 35-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wiedmann et al (5,747,001) in view of Desai et al (US 20070117862) and as evidenced by Verrecchia (6,139,870).

Wiedmann et al teach aerosols containing droplets of an aqueous **dispersion** of nanoparticles of insoluble **beclomethasone** particles having a surface modifier on the surface thereof. Representative examples of surface modifiers include gelatin, benzalkonium chloride, PVA, sorbitans, etc (see col. 3, line 30 to col. 4, line 45). A suitable surfactant is **tyloxapol** (see col. 4, lines 49-60), the particles are preferably less than 400 nm in size, or more preferably less than 250 and most preferably **less than 100 nm** in size (see col. 6, lines 8-15 and col. 10, lines 25-35). The process of making such nanoparticles includes attrition and **filtration** (see col. 7, lines 18-21). It is disclosed that the concentration of the beclomethasone in the liquid medium can vary from about 0.1 to 60%, and preferably from 5-30% (w/w) (see col. 6, lines 19-22). Wiedmann discloses that the surface modifiers can be present in the formulation in an amount from 0.1-90% or preferably from 20-60% based on the total weight of the dry particles (see col. 6, lines 23-28 and col. 10, lines 40-55). Wiedmann discloses filtration, but lacks teachings on sterile filtration.

Desai et al teach formulations for in vivo delivery of pharmacological agents in which the pharmacologically active agent is delivered in the form of suspended particles. There is also provided, a process of preparing unusually small **nanoparticles** of less than 200 nm in diameter, which can be **sterile-filtered**, through a 0.22 micron filter (see [0051]). Desai et al disclose methods for the preparation of substantially water insoluble pharmacologically active agents for in vivo delivery, said method comprising, combining an organic solvent having said active agent dissolved therein, water, a surfactant and a co-surfactant that spontaneously form a micro-emulsion and removing said organic solvent to yield a suspension of nanoparticles of said active agent in said water (see [0093] to [[0100]). It is further disclosed that insoluble active agents include inhalant corticosteroids such as beclomethasone dipropionate and budesonide (see [0122] and [0146]).

Examples **4, 5 and 8** disclose a nanoparticle formation wherein the dispersion is sterile filtered.

Verrecchia discloses that "It has now been found, and this forms the subject of the present invention, that particles can be prepared, 95% of which have an average diameter of less than 100 nm, and more specifically have an average diameter of between 20 and 75 nm, and which can thus be subjected to a sterile filtration on 0.22 um filters without a loss in yield. These particles are moreover more stable than those which could be obtained according to the prior art and can be lyophilized without leading to any phenomenon of particle agglomeration" (see col. 1, lines 26-35). Verrecchia also

discloses that "the nanoparticles thus obtained may be filtered without giving rise to problems of caking together and in good yields" (see col. 2, lines 53-57).

All sterile filtered formulations are expected to be free of contaminants. Thus the newly added limitation of "free from biological contaminants" is met.

With regards to the limitation "consisting of" in claim 35, Wiedmann teaches that the nanoparticles can be surface modified with any of the listed surface modifying agents such as polymers, Tween™, tyloxapol, casein, gelatin, celluloses, dextran, lecithin, etc (see col. 3). Desai also teaches that nanoparticles surface modifies with a stabilizing agents such as proteins are suitable. Desai also recites that a number of biocompatible polymers can be used in the formation of said particles such as dextrans, celluloses, starch, alginates, lipoproteins, etc (see e.g. [0174]). Thus, the claims would have been obvious because the substitution of one known element for another would have **yielded predictable results** to one of ordinary skill in the art at the time of the invention.

With regard to new claims 36-37, the claims are written in a product-by-process format. According to MPEP 2113 [R-1], product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps. Therefore, claims 36-37 are taught by the cited references.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to have implemented the sterile filtration method as taught by Desai

et al in the formulations and process of Wiedmann, since Wiedmann teaches filtration of nanoparticles of beclomethasone and tyloxapol. Thus, one of ordinary skill in the art would have been motivated to implement sterile filtration of Desai et al instead of simple filtration of Wiedmann because sterilized formulations are safer and beneficial to recipients. In other words, the claims would have been obvious because the technique for improving a particular product was part of the ordinary skill in the art, in view of the teaching of the technique for improvement in other situations. Specifically, it is shown that sterile filtration of solid dispersions of nanoparticles in liquid mediums is known in the art (as taught by Desai et al). Weidmann teaches the formulations.

Claims 1-7, 9-11, 13-14 and 35-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wood et al (WO 9625918) in view of Desai et al (US 20070117862) and as evidenced by Verrecchia (6,139,870).

Wood et al teach aerosols containing droplets of an aqueous **dispersion** of nanoparticles of insoluble **beclomethasone** particles having a surface modifier on the surface thereof. Representative examples of surface modifiers include gelatin, benzalkonium chloride, PVA, sorbitans, etc (see pages 6-7). A suitable surfactant is **tyloxapol** (see page 8), the particles are preferably less than 400 nm in size, or more preferably less than 250 and most preferably **less than 100 nm** in size (see page 16). The process of making such nanoparticles includes attrition and **filtration.** It is disclosed that the concentration of the beclomethasone in the liquid medium can vary

from about 0.1 to 60%, and preferably from 5-30% (w/w) (see examples). Wood et al discloses that the surface modifiers can be present in the formulation in an amount from 0.1-90% or preferably from 20-60% based on the total weight of the dry particles. Wood et al discloses filtration, but lacks teachings on sterile filtration.

Desai et al, discussed above, teaches sterile filtration of dispersions of nanoparticles.

All sterile filtered formulations are expected to be free of contaminants. Thus the newly added limitation of "free from biological contaminants" is met.

With regards to the limitation "consisting of" in claim 35, Wood et al teaches that the nanoparticles can be surface modified with any of the listed surface modifying agents such as polymers, Tween™, tyloxapol, casein, gelatin, celluloses, dextran, lecithin, etc (see cols. 4-5). Desai also teaches that nanoparticles surface modifies with a stabilizing agents such as proteins are suitable. Desai also recites that a number of biocompatible polymers can be used in the formation of said particles such as dextrans, celluloses, starch, alginates, lipoproteins, etc (see e.g. [0174]). Thus, the claims would have been obvious because the substitution of one known element for another would have **yielded predictable results** to one of ordinary skill in the art at the time of the invention.

With regard to new claims 36-37, the claims are written in a product-by-process format. According to MPEP 2113 [R-1], product-by-process claims are not limited to the

manipulations of the recited steps, only the structure implied by the steps. Therefore, claims 36-37 are taught by the cited references.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to have implemented the sterile filtration method as taught by Desai et al in the formulations and process of Wood et al, since Wood et al teach filtration of nanoparticles of beclomethasone and tyloxapol. In other words, one of ordinary skill in the art would have been motivated to implement sterile filtration of Desai et al instead of simple filtration of Wood because sterilized formulations are safer and beneficial to recipients. In other words, the claims would have been obvious because the technique for improving a particular product was part of the ordinary skill in the art, in view of the teaching of the technique for improvement in other situations. Specifically, it is shown that sterile filtration of solid dispersions of nanoparticles in liquid mediums is known in the art (as taught by Desai et al). Wood et al teaches the formulations.

Response to Arguments

Applicant's arguments filed 10/29/08 have been fully considered but they are not persuasive.

Applicant argues that "Desai distinguishes and clearly defines what is meant by a surfactant and a surface stabilizing agent". Applicant continues that "Desai does not teach that other surfactants and stabilizing agents are added to the particles. To the contrary, Desai distinguishes his use of the protein albumin as a surface stabilizer from

the prior art's use of "common" surfactants and surface stabilizing agents (e.g., Tweens and Pluronics). To this point, at paragraph [0163] Desai states: "unlike conventional methods for nanoparticle formation, no surfactant (e.g., sodium lauryl sulfate, lecithin, tween 80, pluronic F-68, and the like) is added to the mixture." This not persuasive because 1) Desai is relied upon for its teachings of sterile filtration of dispersions. It has clearly been stated in all of the previous office actions that the nanoparticle dispersions of beclomethasone and/or budesonide and tyloxapol were disclosed by Wiedmann et al and Wood et al. 2) regardless of what the excipients are called by each inventor/author, it is their function that promotes a certain function to the product. In this case Desai is making nanoparticles of paclitaxol and includes a protein such as human serum albumin as the excipient. 3) Wiedmann discloses that tyloxapol may have serve all three functions. The tyloxapol may serve as stabilizer and/or a dispersant, whereas another compound acts as a surface modifier (see col. 4, lines 62-67). 4) Addition of a secondary excipient (surface modifier) is within the scope of instant claims (see e.g. claim 1 (d)). Furthermore, Desai et al does teach that surfactant and co-surfactants can be added to the formulations (see [0094] to [0100]). Suitable surfactants include nonionic surfactants such as Tween™, Span, Triton, Pluronic, etc, and anionic, cationic and zwitterionic surfactants (see [0271] and [0295]). Applicants argument that this taught for oil-in-water emulsions only is not persuasive.

Thus, all is missing from Wiedmann et al or wood et al is sterile filtration. Desai teaches dispersions of nanoparticles that are stabilized using stabilizers such as proteins (see abstract). Desai teaches that particles that are of unusually small size, i.e.

less than 200 nm in diameter, can be sterile filtered through a 0.22 micron filter. It also states that this method in contrast to other methods such as autoclaving are specially suitable for protein containing particles because proteins can not be autoclaved. However this statement is not interpreted (by the Office) as meaning that Desai teaches that only protein rich particles can be sterile filtered. Desai also teaches that other surfactants and stabilizing agents are added to the particles. On the other hand, instant claims require a secondary stabilizing agent added to the particles, which may be a protein (see claims 1 and 9). Thus the combination of Wiedmann et al and Desai et al references would lead one of ordinary skill in the art to the instant claims. Examples 8 and 9 and others (such as 4 and 5 mentioned on the last paper) all while using a different active agent than budesonide or beclomethasone, disclose that if particles less than 200 nm in diameter are formed, they were sterile filtered through a 0.22 micron filter. Thus it is concluded that Desai provides adequate teachings to one of ordinary skill in the art having the nanoparticle dispersions of Wiedmann to sterile filter the particles by passing them through a 0.22 micron filter.

Applicant also argues that "The only working examples which Desai sterilized by filtration includes a single drug bound by protein. Desai only discloses a single dispersion (Example 8 and repeated in Example 9) of isoreserpine particles with albumin-bound protein. The Examiner reads Desai's specification as allowing the use of other active agents and other surface stabilizers in support of the general statement that all nanoparticles less than 200 nm can be sterilized by filtration". While this statement is correct it is not persuasive because again Desai was relied upon for its teachings of

sterile filtration. Based on Desai's teachings and Verrecchia et al, the nanopraticle dispersions comprising particles smaller than 0.2 micron can be sterile filtered, if they do not aggregate or cake (see Verrecchia, columns 1 and 2).

Applicant argues unexpected results and combines the examples of specification in a table (see Remarks, page 16). Applicant states that "The table below summarizes the results presented in the working examples of the specification. As demonstrated by Examples 5, 8, 13, 15, 16, 17 and 18, although a nanoparticulate dispersion having an effective average particle size of less than 200 nm can be obtained, the dispersion cannot be sterilized by filtering through a 0.22 micron filter due to aggregation or other factors. This is itself evidence of the unpredictability in the art of forming stable nanoparticulate dispersions, discussed in more detail below. Accordingly, Applicants have established that there is unpredictability in the art concerning a nanoparticulate dispersion that can be sterile filtered with a filter having a pore size of 0.2 micron or less". Applicant is in a way confirming Examiner's position that formulations that were not successfully filtered, were those that aggregated. This is also in accordance with the general knowledge in the art of sterile filtration (see e.g. Verrecchia). While it is clear from the data (see Specification and Table provided in Remarks), that not all nanoparticle dispersion formulations are successfully sterile filtered, it is clear from the examples in specification and prior art such as Verrecchia, that those formulations that do not cake or aggregate are filterable. One of ordinary skill in the art may not be able to deduce form any set formula whether the formulation is sterile filterable or not but, they know that this is a possibility and would naturally test the formulations. It is then the

Examiner's position that because of all the available teachings in the prior at, a particular combination of an active agent and surface modifier is not a showing of unpredictability. In other words, this the nature of filtration and it is known that formulations may have to be tested.

Thus despite Applicants claim of unpredictability, there is no evidence of unpredictability and it is maintained that the combination of the references cited render instant claims obvious.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINA HAGHIGHATIAN whose telephone number is (571)272-0615. The examiner can normally be reached on core office hours.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Mina Haghighatian/

Mina Haghighatian
Primary Examiner
Art Unit 1616